

RECENT ADVANCES IN
3

RESPIRATORY
MEDICINE

Edited by

David C. Flenley and Thomas L. Petty



Recent Advances in **RESPIRATORY MEDICINE**

NUMBER THREE

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Preface



One of today's greatest challenges for the practising physician lies in the fact that the art continues to expand, whereas the life-time available for absorbing new information remains all too brief. *Recent Advances In Respiratory Medicine—3* aims to help resolve this dilemma by providing concise but authoritative reviews of growing points related to the practice of today's chest physician (or pulmonologist). This volume has now a firm international (if possibly mid-Atlantic) basis, and the minor differences of emphasis and style that thereby result may serve to widen the reader's horizons. As before, the selection of topics (and of authors) is the editor's major task, and still represents their personal choice. The result not only covers areas where new work is important for the clinician for today's problems, as in asbestos-induced lung disease, the adult respiratory distress syndrome, cystic fibrosis in the adult, chronic bronchitis, emphysema, and sleep-disordered breathing, or in lung cancer; but also aims to highlight new understandings of important developments of the pathogenesis of pulmonary disease, as in the role of leukotrienes in bronchial asthma, where advances in drug therapy are imminent, and in applications of broncho-alveolar lavage. New methods of using older drugs, such as the β_2 sympathomimetic agonists or theophyllines in asthma, or in new short course regimens of anti-tuberculosis chemotherapy have great bearing on today's practice. Recognition of the hazards and presentation of drug-induced lung disease is increasingly important, as indicated by the plethora of recent reports that have to be summarized. Respiratory physiologists have now turned their attention to the breathing muscles, and the new knowledge here has relevance for both bedside diagnosis as well as for treatment. All recognize the importance of smoking as a cause of respiratory disease, and the newer knowledge of the anti-protease mechanisms by which this occurs seems set to yield important advances in therapy, although it still seems likely that a major impact on the prevalence of smoking will depend upon both political will and the application of this will through fiscal measures. Better it would be if society were more interested in health and prevention of disease!

Once again, the editors hope that this mixture will inform, hopefully also excite, and may even entertain the reader; but it must surely also sustain the proposal that respiratory medicine is advancing—and that at a rate where both physician and patient are becoming rather breathless!

We thank Mrs H. E. Flenley for compiling the index.

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1. Respiratory muscles

M. Green J. Moxham



INTRODUCTION

The respiratory muscles provide the motive power for breathing. Despite this vital role in respiration, study of their function has been relatively neglected. Duchenne (1867) fully described the actions of the respiratory muscles: he studied animals before and after evisceration and noted the importance of the abdominal contents as a fulcrum for diaphragmatic contractions. In 1925 Rohrer pointed out that breathing consisted of four interlocking processes: (1) movement of body mass by muscular activity to cause a change in volume of the thoracic cavity; (2) movement of lung tissue to cause (3) changes in pressure in the lungs and consequently (4) flow of air in the connecting tubes. Most physiologists and clinicians devote their attention to (4) no doubt partly because disease of the airways is common, and measurements of this function are easy to make. Less time is spent on (2) and (3) and least on the respiratory muscles. Rohrer pointed out that more than a third of the body mass, including the wall of the body trunk, as well as the abdominal and thoracic contents, takes part in respiration. This makes respiratory movements clinically obvious and again emphasizes the importance of the abdomen to respiratory muscle function.

No comprehensive review was attempted until Campbell's classic monograph (1958), which pointed out the importance of the respiratory muscles to physiologists and clinicians. In the last decade there has been a resurgence of physiological interest, which is slowly being applied clinically.

It is now more widely appreciated that the muscles are crucial to effective respiration and occupy a central position in the chain between the respiratory centres and adequate ventilation (Fig. 1.1).

RESPIRATORY MUSCLES IN HEALTH

Anatomy

The main respiratory muscles are the diaphragm, intercostal muscles and muscles of the abdominal wall. Accessory muscles of respiration include the sternomastoid and other muscles of the neck, back and shoulder girdle. All of these, including the diaphragm, are skeletal muscles and their fine structure is little if any different from the more extensively studied limb skeletal muscles. They thus contain a mixture of the two muscle fibre types: type I slow-twitch fatigue-resistant fibres (roughly corresponding to 'red' fibres) whose energy is predominantly provided by oxidative pathways (and therefore dependent on oxygen and hence blood supply); and type II fast-twitch fibres most of which (type IIB) fatigue quickly and involve glycolytic energy pathways ('white' fibres). However some relatively fatigue-resistant type II

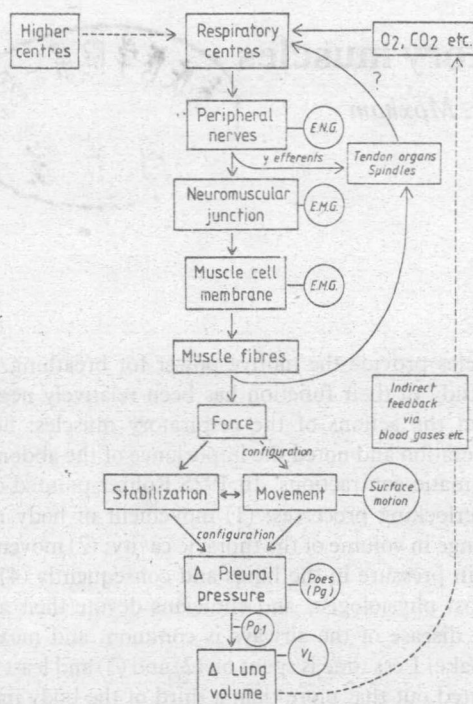


Fig. 1.1 Breathing pathway. This diagram illustrates the complexity of the pathway between the respiratory centres and change in lung volume. The respiratory muscles are central to this chain. The importance of the configuration of the system in the translocation of muscle force into change in pleural pressure is emphasized and it can be seen how indirectly respiratory muscle activity causes changes in lung volume. Established feedback mechanisms are relatively sparse. It will be noted that the techniques for studying this system (circled) are often indirect and difficult to interpret. They include the phrenic neurogram (ENG), electromyogram (EMG), measurement of surface motion (see text), respiratory pressures (Poes, $P_{0.1}$) and lung volume change (V_L).

fibres (IIA) are fast-twitch, and have both oxidative and glycolytic pathways. Fibre types can be further subdivided with specific histochemical staining, presumably related to their different functions (Walton, 1982). In general slow fibres provide for endurance of muscles, whereas fast fibres allow brief intensive activity. Although it might be thought that endurance throughout life was the prime function of the respiratory muscles, brief intense activity is also important and the admixture of the two fibre types reflects this dual function. There appear to be about 55% of type I and 45% of type II fibres in the adult diaphragm (Lieberman et al, 1973) although the studies have been few and there is considerable variability between subjects. It is not known whether fibre type composition is fixed or can be altered by activity. Although there is no evidence that training can affect fibre type, the physiological characteristics and size of fibres can be altered by suitable training regimens (Faulkner et al, 1979).

An important property of skeletal muscle is its length: tension relationship. For a given neural output a muscle achieves maximum tension at around its resting length. As length either diminishes or increases the tension achieved tends to fall off. The

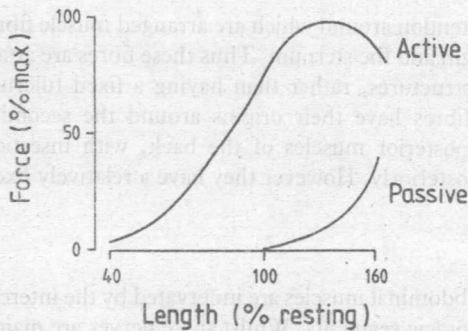


Fig. 1.2 Diaphragm length: tension relationship measured in anaesthetized dogs. Passive tension develops when the muscle is stretched from its resting length (100%). The active relationship was obtained during tetanic supramaximal phrenic nerve stimulation. Maximal active tension was obtained at approximately 25% above resting length, in contrast to other skeletal muscles whose maximum tension occurs at resting length. Furthermore there is appreciable tension at 50% resting length, whereas this is zero in skeletal muscle. This gives the diaphragm a broad range of effective muscle length. Nevertheless the tension achieved is greatly influenced by its length and hence chest wall configuration. Modified by permission from Kim et al, (1976).

isolated diaphragm strips show this classical length: tension relationship, but with a broader optimal range than in limb muscles (Fig. 1.2).

The respiratory muscles have a generous blood supply. The diaphragm differs from other skeletal muscles in that its arterial supply is distributed across its surface and only the smaller arterioles penetrate the muscle substance. This is presumably possible because the diaphragm is thin and flat, but it has the important consequence that the blood supply is less likely to be constricted during contraction of the muscle, as occurs in large limb muscles. Both surfaces of the diaphragm are also richly supplied with lymphatics.

The intercostal muscles are arranged diagonally between the ribs. The external intercostal muscles slope downwards and forwards. Their contraction causes expansion of the ribcage by lifting the ribs with reference to the neck and cervical spine, and causing rotation about their articulations with the thoracic vertebral bodies, the 'bucket handle' mechanism. Whilst simple in outline, this mechanism is complex in detail. Normally the anterior ends of the ribs are relatively free-floating with flexible junctions to the sternum via the costal cartilages. The sternum itself moves anteriorly and upwards with inspiration. The internal intercostals subserve active expiration, when necessary, as their fibres run downwards and postero-laterally between the ribs.

The anterior abdominal muscles are important muscles of respiration, being involved in both inspiration and expiration. In addition to the powerful rectus muscle there are muscle layers running diagonally and laterally around the abdomen, whose overall effect is to cause powerful abdominal constriction. Expansion of the abdominal wall appears to occur by relaxation of the muscles and the action of gravity, or by contraction of the diaphragm.

The diaphragm is a complicated muscle anatomically and physiologically. The resurgence of interest in its physiology has directed workers to its anatomy, which appears critical to its function. The main part of the diaphragm is dome-shaped with a

large central fibrous tendon around which are arranged muscle fibres originating from the lower costal margin and the sternum. Thus these fibres are attached at each end to potentially moving structures, rather than having a fixed fulcrum. In addition the powerful vertebral fibres have their origins around the second and third lumbar vertebrae, and the posterior muscles of the back, with insertion into the central diaphragm tendon posteriorly. However they have a relatively fixed fulcrum, at their vertebral end.

Innervation

The intercostal and abdominal muscles are innervated by the intercostal nerves arising from the 1st–12th thoracic segments. Whilst these nerves are mainly motor they also contain afferent fibres. These muscles are well supplied with muscle spindles, tendon organs and Paccinian corpuscles. The lower intercostal nerves, supplying the abdominal muscles, pass through the diaphragm as they travel inferiorly and give off a few fibres to it. These are probably mainly sensory.

The diaphragm is innervated by the phrenic nerve, originating in the 3rd, 4th and 5th cervical segments. There has been a tendency to deny the existence of sensory input from the diaphragm. This may have been based on the histological finding that there are more tendon organs than spindles in the animal diaphragm and few of either compared to other skeletal muscles. On the other hand afferent fibres have been identified in the phrenic nerve of cats and afferent traffic recorded. Since the diaphragm tends to contract uniformly it may be that relatively few sensory organs are sufficient to signal its length and tension, compared to the larger number required for fine limb movements.

Physiology

Techniques for study

The respiratory muscles are more difficult to study than most other skeletal muscles because of their complex arrangement and inter-relationships, and as their function is to generate pressure changes within the thorax, rather than the more simply measured forces and movements required of limb muscles. In the last decade workers have tried to analyse their function by making indirect measurements (Fig. 1.1).

Movements of the chest wall have long been studied by pneumography but Konno & Mead (1966) introduced magnetometers, pairs of electro magnets, one to generate and one to receive electro magnetic impulses. The signals can be processed to indicate the distance between the two magnetometers. This technique has been used to study the relative movements of the abdomen and ribcage under a variety of circumstances. More recently impedance pneumographs have been introduced, on the principle that the electrical impedance of a wire zig-zagged around the torso varies with the circumference of the torso. Such pneumographs have been incorporated into vests over the ribcage and abdomen (Respirtrace). These have the advantage of convenience, but do not differentiate between anterior and lateral motion of the torso, which can sometimes be important. They have been used as a non-invasive method of detecting and monitoring volume change in the lungs, by converting the circumferential change of the ribcage and abdomen in to a volume equivalent. This technique is attractive but has the grave disadvantage that the volume equivalents of the two

compartments can alter substantially with change in posture, lung volume or shape of the diaphragm. More sophisticated techniques are being developed for studying movements of the ribcage and abdomen, for example by projecting stripes of light onto the torso (Denison et al, 1982). This may allow analysis of the fine detail of chest wall movements.

Change in volume at the mouth obviously reflects respiratory muscle activity, but is a complicated integration of the whole process of breathing, and is thus a relatively non-specific measurement. Under controlled circumstances, however, it can be a useful reflection of respiratory muscle activity both physiologically and in clinical practice. More specifically the mean inspiratory flow rate (tidal volume divided by the duration of inspiration, V_T/T_i) reflects central respiratory drive and the respiratory muscle response. T_i divided by the total time of a breathing cycle (T_i/T_{tot}) gives an indication of the time of active inspiration, the duty ratio (Derenne et al, 1976).

Pressures

The function of muscles is to generate force, but direct measurement of the forces generated by respiratory muscles has not been possible in intact man. However the forces generated by the respiratory muscles are converted into pressure changes within the thorax (Fig. 1.3). Oesophageal pressure reflects intra-thoracic pressure

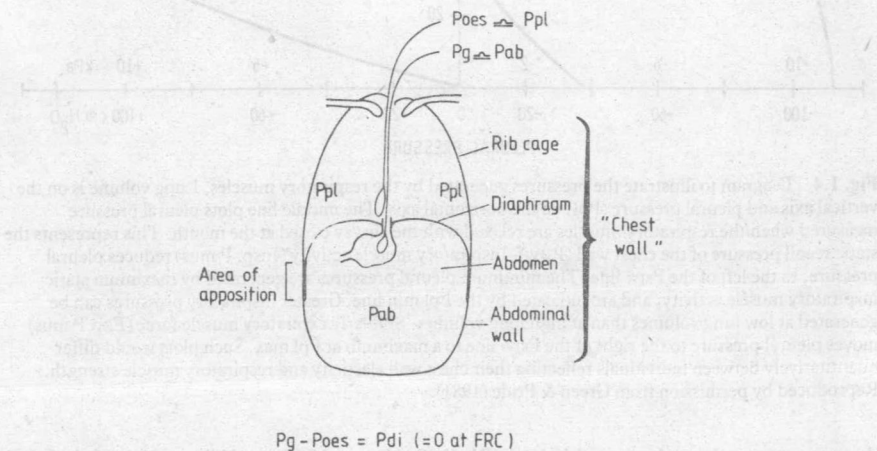


Fig. 1.3 Diagram to illustrate some features of the respiratory muscles. Oesophageal pressure (P_{oes}) and gastric pressure (P_g) are measured by balloons on fine catheters passed into the middle to lower oesophagus and stomach. These give a reasonable approximation to pleural pressure and abdominal pressure respectively which can not be measured directly. Transdiaphragmatic pressure (P_{di}) is obtained by subtraction. Perhaps confusingly the 'chest wall' is defined as all the structures outside the lungs taking part in breathing movement (Bartels et al, 1973). Note the extent to which the ribcage spans the abdomen due to an extensive 'area of apposition' of the diaphragm to the lower ribcage at FRC.

under most conditions and can be relatively easily measured by passing a balloon into the oesophagus. Abdominal pressure can also be measured by passing a balloon into the stomach and the difference between the two is a measure of the pressure across the diaphragm, transdiaphragmatic pressure. Analysis of pressure changes combined with movements in a variety of physiological and clinical circumstances has allowed

further analysis of respiratory muscle function. Milic-Emili et al (1975) pointed out that the pressure generated at the mouth during the first one-tenth of a second of an inspiration against a closed shutter reflects respiratory muscle output, before there is time for compensatory mechanisms to become effective or lung pathology to influence the pressure. This is useful for looking at overall muscle function, but does not indicate which muscles are providing the pressure and how. Similarly measurements of the maximum pressure which can be generated statically against an obstruction can give an indication of overall respiratory muscle strength. Maximum mouth pressure turns out to be greatest for expiration when the effort is made at high lung volume, and for inspiration when the effort is made at low lung volume (Fig. 1.4). Normal values for

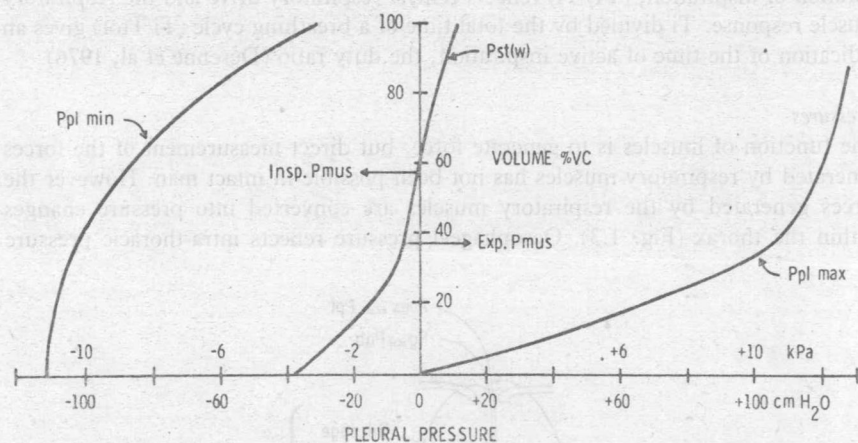


Fig. 1.4 Diagram to illustrate the pressures generated by the respiratory muscles. Lung volume is on the vertical axis and pleural pressure (Ppl) on the horizontal axis. The middle line plots pleural pressure measured when the respiratory muscles are relaxed with the airway closed at the mouth. This represents the static recoil pressure of the chest wall (Pstw). Inspiratory muscle activity (Insp. Pmus) reduces pleural pressure, to the left of the Pstw line. The minimum pleural pressures are generated by maximum static inspiratory muscle activity, and are indicated by the Ppl min line. Greater inspiratory pressures can be generated at low lung volumes than at high lung volumes. Similarly expiratory muscle force (Exp. Pmus) moves pleural pressure to the right of the Pstw line to a maximum at Ppl max. Such plots would differ quantitatively between individuals reflecting their chest wall elasticity and respiratory muscle strength. Reproduced by permission from Green & Pride (1981).

these pressures have been published (Black & Hyatt, 1969) and they are useful global tests of respiratory muscle function although they are dependent on full co-operation by the subject, and on normal mouth and cheek muscles.

Electromyography

Electromyography of the respiratory muscles has proved technically difficult and a problem to interpret. Intercostal activity can be detected by needle electrodes placed in the intercostal muscles, although it can be difficult to distinguish internal and external muscle activity. Diaphragmatic EMG can be detected by electrodes suitably placed at the lower costal margin over the insertion of the diaphragm, or by electrodes on a catheter connected to a balloon passed into the lower oesophagus (Derenne et al, 1978). These techniques give useful information as to whether the muscles involved

are electrically active, but the translation of this into force or pressure equivalents is hazardous.

Normal function

During quiet breathing the respiratory system is relaxed at resting end expiration with little, if any, muscle activity. Inspiration is achieved by expanding the thoracic cavity and lungs by muscular work (Fig. 1.5). The diaphragm contracts and may descend, or

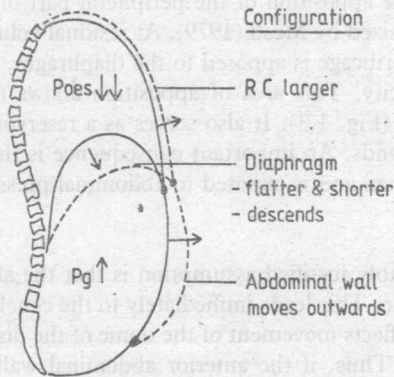


Fig. 1.5 Illustrates the changes on a normal inspiration to TLC with an increase in gastric pressure (P_g), a reduction in oesophageal pressure (P_{oes}) and hence an increase in transdiaphragmatic pressure.

elevate the ribcage, or both. The external intercostal muscles contract to raise the ribcage. Expiration is partly passive, the elasticity of the lungs and chest wall tending to return the system to FRC. In addition there may be active contraction of the internal intercostals and abdominal muscles. Respiratory movement has been the subject of intense study over the past decade in an attempt to define more accurately the relative contributions of the different parts, in different situations, revealing a complexity which has served in part to clarify, and in part simply to pose new questions.

Configuration

One of the most helpful concepts to have been established is the importance of the length and shape, usually termed 'configuration' of the respiratory muscles, and particularly the diaphragm (Fig. 1.5). Marshall (1962) pointed out that for a given fibre contraction, the more curved the diaphragm, the greater is the pressure difference created across it (an example of the Laplace relationship). In the extreme an entirely flat diaphragm would obviously create no pressure difference across it. Thus at high lung volumes a given neural output would be likely to cause less change in transdiaphragmatic pressure than at low lung volumes. However, it is now believed that the normal diaphragm probably has a reasonably similar shape at different lung volumes, moving up and down more like a piston than a sheet of rubber. Nonetheless, it is still likely to generate less pressure for a given neural input at higher lung volumes because of its length:tension relationship (Fig. 1.2). As the diaphragm shortens below its resting length the contractile force achieved for a given neural

output becomes less, and hence less transdiaphragmatic pressure is generated. In the supine posture gravity tends to cause the abdominal contents to push the diaphragm upwards, keeping its configuration relatively constant, even when it contracts during inspiration. However, in the upright posture gravity tends to cause the abdominal contents to fall forwards but the abdominal muscles prevent this and tend to keep diaphragm configuration constant. Thus the abdominal muscles may play an important part in inspiration, and should not be viewed as simply expiratory muscles.

The importance of the apposition of the peripheral part of the diaphragm to the ribcage has been emphasized by Mead (1979). At residual volume more than half the total surface area of the ribcage is apposed to the diaphragm, but this nearly falls to zero at total lung capacity. This area of apposition allows the diaphragm to pull upwards on the ribcage (Fig. 1.3). It also serves as a reservoir for surface area and volume as the lung expands. An important consequence is that a proportion of the ribcage spans the abdomen and is exposed to abdominal pressure.

Chest wall movement

An important and probably justified assumption is that the abdominal contents are effectively incompressible. This leads immediately to the conclusion that movements of the abdominal wall reflects movement of the dome of the diaphragm: indeed these are inextricably linked. Thus, if the anterior abdominal wall moves outwards the diaphragm has descended (Fig. 1.5). Conversely the diaphragm cannot move downwards without outward motion of the abdominal wall. It should be noted, however, that this does not allow conclusions about the state of contraction of the diaphragm, but only its motion. Indeed the diaphragm can move downwards without contracting (if there is relaxation of the abdominal muscles in the upright posture), and can contract without moving downwards (as for example if the abdominal muscles also contract strongly). However, this relationship allows physiological analysis of diaphragmatic motion and can be an important clinical sign.

When the diaphragm contracts during inspiration it tends to displace the abdominal contents downwards and the anterior abdominal wall outwards (Fig. 1.5). Abdominal pressure (measured as gastric pressure) rises, partly because of the impedance to movement provided by the abdominal contents and abdominal wall, but also as a result of abdominal muscle contraction. The diaphragm is inserted at its circumference into the lower costal margin, so that if it cannot descend due to a rise in abdominal pressure, the tension developed in these fibres pulls the lower costal margin upwards. This upwards pull moves the ribs upwards, and because of their articulations also moves them outwards, so causing the ribcage to expand and pleural pressure to fall. Thus the diaphragm uses abdominal pressure as a fulcrum to expand the ribcage. It can be seen that both actions of the diaphragm: (1) descent of the dome, and (2) elevation of the ribcage, cause a fall in pleural pressure which causes inspiration. In analysing these relationships Goldman & Mead (1973) concluded that the pressure rise in the abdomen on diaphragmatic contraction was equal to the reduction in pleural pressure achieved by the diaphragm's tendency to elevate and expand the ribcage. The quantitative aspects of this analysis are being questioned, particularly by Macklem (1979). It is possible that this debate will be resolved by the suggestion of De Troyer et al (1981) that the diaphragm acts differently in its two parts: the vertebral part with its fixed insertion and the costal part with its floating

insertion in the costal margin. However, Goldman & Mead's analysis certainly served to emphasize the importance to ribcage expansion of the normal rise in abdominal pressure during inspiration.

From the above analysis it may be seen that the diaphragm is probably the most important muscle of respiration. However, the additional importance of the abdominal muscles and the intercostal muscles is widely agreed, although the quantitative contribution of each muscle group to respiration in health, let alone in disease, is still debated. It seems very likely that the contributions may vary from time to time, and with changes in posture, exercise and abnormal environments such as altitude, diving and space travel.

RESPIRATORY MUSCLES IN DISEASE

Neuromuscular disease

Diaphragm paralysis

Unilateral paralysis of the diaphragm is not infrequent, and is easily suspected on chest X-ray and confirmed by fluoroscopy. Interestingly it appears to cause little clinical or physiological abnormality, although some reduction of ventilation and perfusion in the associated lung, with a mild reduction of arterial PO_2 have been described.

By contrast bilateral paralysis, or weakness, of the diaphragm is less common, has important clinical and physiological effects, but is easily overlooked (Newsom Davis et al, 1976). It can occur in association with generalised neuromuscular disorders such as motor neurone disease, myopathies and myasthenia, or following damage to the phrenic nerves in polyneuritis, (diphtheria, polio, Guillain-Barré) and following trauma at surgery. Such patients show impressive orthopnoea, without evidence of heart disease. Indeed they may be able to walk relatively freely, if slowly, but become grossly dyspnoeic within 15–20 seconds on lying supine. This is due to the important interaction of gravity and the respiratory muscles. When the patient is upright inspiration occurs by contraction of the external intercostal muscles and elevation of the ribcage (Fig. 1.6). At the same time the abdominal muscles relax and the abdominal wall tends to move outwards, due to the effect of gravity on the abdominal contents. Expiration is active, with contraction of the internal intercostal muscles to diminish ribcage size, and contraction of the abdominal muscles to constrict the abdominal wall which moves the abdominal contents inwards, and to some extent upwards. These manoeuvres result in reasonable ventilation and moderate exercise tolerance in the upright posture, despite the absence of diaphragmatic function. It may be noted that the action of the abdominal muscles, with outward movement of the abdominal wall during inspiration tends to cause the diaphragm to move downwards during inspiration. Thus fluoroscopy of the diaphragm in the upright posture may reveal apparently normal motion of the diaphragm, which is frequently misinterpreted as representing diaphragm contraction. Sniffing may elicit paradoxical motion of the diaphragm, but even this can be difficult to identify when upright. However, when supine, respiratory movements are grossly abnormal (Fig. 1.6), with the external intercostals expanding the ribcage on inspiration, but abdominal contents are then sucked up into the ribcage, aided rather than hindered by gravity. Relaxation